REMARKS

Status of the Claims

The claims currently pending in the above-identified application are claims 1-25, and Claims 14-20 have been withdrawn from consideration. Claims 1, 8, and 21-25 have been amended.

The Rejections Under 35 U.S.C. § 102

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 102(b) as being anticipated respectively by U.S. Patent Nos. 5,504,074 to D'Amato et al. ("*D'Amato*"), 5,521,168 to Clark ("*Clark*"), and 5,643,900 to Fotsis et al. ("*Fotsis*"). In view of the above amendments, Applicants respectfully request these rejections be withdrawn.

The arguments set forth in Applicants' Response filed December 14, 2001 with respect to *D'Amato*, *Clark*, and *Fotsis* are incorporated herein by reference and are not repeated here for brevity. In addition, Applicants submit the following comments.

As stated in Applicants' written description at page 2, lines 16-27, steroid **contaminants**, such as, estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone, have estrogenic or carcinogenic effects which **counteract** the effects of 2-methoxyestradiol. Further, the U.S. Patent and Trademark Office ("PTO") takes the position that even though these references are silent to the purity of 2-methoxyestradiol discussed therein, it can be assumed that the 2-methoxyestradiol is pure. However, there is absolutely no basis upon which the PTO can make this assumption, particularly given that the cited references fail to recognize the problem caused by steroid contaminants in 2-methoxyestradiol pharmaceutical compositions. Since the cited references fail to recognize the problem, it cannot be assumed that the 2-methoxyestradiol is pure and the steroid contaminants are not present. The PTO has failed to provide any reference showing a 2-methoxyestradiol pharmaceutical composition as claimed, which it is obligated to do. The Sigma Certificate of Analysis filed as Exhibit A in the above-identified response (filed December 14, 2001) shows that the 2-methoxyestradiol sold by the Sigma Chemical Company was not pure. Table 1, page 18 of Applicants' written description shows that commercially available 2-methoxyestradiols are not pure and contain the steroid

contaminants described above. Moreover, none of the cited references recognize that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone are contaminants which have counteracting effects to 2-methoxyestradiol. Accordingly, it cannot be assumed that the 2-methoxyestradiols of the cited references are pure.

None of the cited references teach or suggest a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC. Further, none of these references teach or suggest a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone. In view of the above amendments, Applicants respectfully assert that the rejections under 35 U.S.C. § 102(b) have been overcome and should be withdrawn.

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,200,966 to Stewart et al. ("*Stewart*"). In view of the above amendments, Applicants respectfully request these rejections be withdrawn.

Stewart is directed to the use of 2-methoxyestradiol, 2-hydroxyestradiol, and 4-methoxyestradiol, as well as other estradiol derivatives, to modulate airway remodeling by inhibiting inflammation and/or smooth muscle cell proliferation of the airway wall. As stated at column 10, lines 13-17, the source of 2-methoxyestradiol was lot 83H4065, Sigma, USA. The Certificate of Analysis for lot 83H4065 was attached as Exhibit "A" to the above-identified Response. As indicated by the Certificate of Analysis, the purity as determined by **HPLC** of the 2-methoxyestradiol used by *Stewart* was only 98.0%. *Stewart* fails to teach or suggest a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC.

Further, *Stewart*, like the references cited above, fails to recognize the problem of steroid contaminants in 2-methoxyestradiol pharmaceutical compositions. Actually, *Stewart* promotes the use of the steroid contaminants 2-hydroxyestradiol and 4-methoxyestradiol, thereby **teaching away** from removing steroid contaminants in 2-methoxyestradiol pharmaceutical

compositions. Since *Stewart* fails to recognize the problem, *Stewart* has no motivation to remove the steroid contaminants. Thus, it cannot be assumed that the 2-methoxyestradiol taught by *Stewart* is pure and the steroid contaminants are not present. *Stewart* fails to teach or suggest a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone. The PTO has failed to provide any reference showing a 2-methoxyestradiol pharmaceutical composition as claimed, which it is obligated to do. In view of the above amendments, Applicants respectfully assert that the rejections under 35 U.S.C. § 102(e) have been overcome and should be withdrawn.

For a reference to qualify as prior art under 35 U.S.C. § 102, it is well established that the reference alone **must teach each and every element** of the claimed invention. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). (Emphasis added.) **Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference.** (Emphasis added.) See *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984). Since *D'Amato*, *Clark*, *Fotsis*, and *Stewart* respectively are either silent as to the purity of the 2-methoxyestradiol, to the steroid contaminants, or both, these missing elements, may not be assumed. Since these references fail to teach each and every element of the claimed invention, none of these references can anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejections of Claims 1-13 and 21-25 under 35 U.S.C. § 102(b) and (e) be withdrawn.

The Rejections Under 35 U.S.C. § 103(a)

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *D'Amato, Clark, Fotsis*, or *Stewart*. These references are discussed above and for brevity such discussion is incorporated here. Applicants respectfully request that this rejection be withdrawn in view of the above amendments.

The PTO states that "obtaining a compound containing as little as possible of [an] impurity would be obvious to the skilled artisan." However, this statement fails to recognize

what the skilled artisan would consider to be an "impurity" in a pharmaceutical composition of 2-methoxyestradiol. As stated above, the Applicants demonstrated that commercially available 2-methoxyestradiols **did** contain the steroid contaminants. This indicates that the skilled artisan does not recognize that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone are contaminants or impurities in 2-methoxyestradiol compositions. Actually, the skilled artisan is motivated by the cited references not to consider the steroid contaminants as impurities. As discussed above and in the above-identified Response, each of the cited references employs one or more of the steroid contaminants and **fails to recognize them as impurities**. Accordingly, the skilled artisan would not be motivated to remove the steroid contaminants from 2-methoxyestradiol compositions. Further, there is no suggestion in the cited references to do so, since the references fail to recognize that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone are impurities. Thus, it cannot be assumed that the 2-methoxyestradiol of the cited references is pure. Additionally, the PTO states that the phrase "less than" implies that the compound may be absent and the prior art compound does not have to contain any of the other compounds recited by Applicants. However, there are no references cited by the PTO which show that such compounds, that is, the steroid contaminants, are absent.

Accordingly, none of the cited references either alone or in combination suggest a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC. Further, none of these references either alone or in combination suggest a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone.

Further, neither *D'Amato*, *Clark*, nor *Fotsis* state the degree of purity or the source of the 2-methoxyestradiol employed in the respective reference. Accordingly, since none of the experimental sections of these references discuss how the 2-methoxyestradiol was made, it may be reasonably concluded that commercially available 2-methoxyestradiol was employed, which, as Applicants teach, has a purity no greater than 98% as determined by HPLC. Even

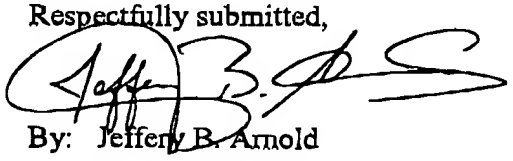
further, none of the cited references teach or suggest a 2-methoxyestradiol composition containing less than 0.03 % estradiol, 0.02% or less 2-hydroxyestradiol, 0.02% or less 4-hydroxyestradiol, 0.02% or less 4-methoxyestradiol, and less than 0.02% estrone, respectively. Actually, as discussed above, each of the references employs one or more of these compounds and fails to recognize them as impurities.

None of the cited references either alone or in combination teach or suggest all of the limitations of the claimed invention. Accordingly, Applicants respectfully request that the rejection of Claims 1-13 and 21-25 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

The foregoing is submitted as a full and complete Response to the Office Action mailed January 31, 2002, and early and favorable reconsideration of the claims is requested. Applicants respectfully assert that the rejections of the claims have been addressed and overcome. Applicants further assert that all claims are in a condition for allowance and request that a timely notice of allowance be issued. If the Examiner believes any informalities remain in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 949-2400 is respectfully solicited.

Respectfully submitted,



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Version With Markings to Show Changes Made

Please amend the claims by deleting the bracketed word(s) and inserting the underlined word(s) as indicated.

1. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC.

8. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98.0% and containing less than 0.03% estradiol and less than 0.02% estrone.

21. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

protecting the 3- and 17-hydroxyl groups of estradiol;

reacting the protected estradiol with bromine and acetic acid to produce a 2-brominated derivative of estradiol;

reacting the 2-brominated derivative of estradiol with sodium methoxide in the presence of a copper catalyst;

removing the protecting groups on the 3- and 17-hydroxyl groups to produce 2-methoxyestradiol; and

purifying the 2-methoxyestradiol using liquid chromatography on an adsorption/partition medium with a solvent system comprising a polar and a nonpolar solvent.

22. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

ring-brominating estradiol by reacting estradiol with bromine in the presence of acetic acid to produce a ring-brominated intermediate;

reacting the ring-brominated intermediate with sodium methoxide in the [present] presence of a copper catalyst to produce 2-methoxyestradiol; and

purifying the 2-methoxyestradiol using liquid chromatography on an adsorption/partition medium with a solvent system comprising a polar and a nonpolar solvent.

23. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

protecting the 3- and 17-hydroxyl groups of estradiol;

reacting the protected estradiol with nitric acid and acetic acid to produce a 2-nitro derivative of estradiol;

reducing the 2-nitro derivative of estradiol to produce the corresponding 2-amino derivative of estradiol;

reacting the 2-amino derivative of estradiol under Sandmeyer conditions to produce a 3-,17-hydroxyl protected 2-methoxyestradiol; and

removing the protecting groups on the 3- and 17-hydroxyl groups to produce 2-methoxyestradiol.

24. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

protecting the 3-hydroxyl group of estrone;

reacting the protected estrone with nitric acid and acetic acid to produce a 2-nitro derivative of estrone;

reducing the 2-nitro derivative of estrone to produce the corresponding 2-amino derivative of estrone;

reacting the 2-amino derivative of estrone under Sandmeyer conditions to produce a 3-hydroxyl protected 2-methoxyestrone;

removing the protecting group on the 3-hydroxyl group to produce 2-methoxyestrone; and

reducing the 17-keto group of 2-methoxyestrone to produce 2-methoxyestradiol.

25. A pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98% and containing less than 0.03% estradiol and less than 0.02% estrone produced by the process comprising:

brominating estradiol in the presence of acetic acid to produce a mixture of ring-brominated estradiols;

isolating 2-bromoestradiol from the mixture of estradiols; and

reacting the 2-bromoestradiol with sodium methoxide in the presence of a copper catalyst to produce 2-methoxyestradiol.